REMARKS

Claims 1-4 and 6-22 are currently pending in the above-identified application. Claims 3 and 16 have been amended. Support for these amendments is identified in the following remarks. No new matter has been added by these amendments.

Information Disclosure Statement

The Examiner states that the Information Disclosure Statement filed on January 31, 2002, did not contain copies of the non-patent literature. However, Applicants note that these items were provided in the parent application, USSN 09/213,052 (now U.S. Patent 6,432,641) and under 37 CFR §1.98(d)(1) copies are not required to be filed in the present continuation-in-part application. However, Applicants are attempting to locate additional copies of these references which will be submitted under separate cover.

Formal Drawings

The Examiner has indicated that Fig. 2 is improperly labeled. Attached hereto is are two sheets of drawings which include both a replacement sheet and an annotated sheet showing changes.

Claim Rejections under 35 USC §112, 2d Paragraph

Claims 3 and 16 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claims 3 and 16 are vague and indefinite in that the metes and bounds of a "metal-containing nucleic acid expresses an antigenic protein" are unclear. These claims have been amended to better indicate that the metal-

containing nucleic acid "encodes" an antigenic protein, as is understood in the art, thereby obviating the rejection.

Claim Rejections under 35 USC §112, 1st Paragraph

Claims 1-4 and 6-22 are rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the enablement requirement. The examiner analyzes the claimed invention from the perspective of factors enunciated in *In re Wands* and *Ex parte Forman*, and these points are addressed by Applicants in the order presented in the Office Action.

Under "scope of the invention," it is said that the base claim 1 reads on a method of gene therapy, and that the steps of gene therapy "exacerbate a complex method." Although it is not understood exactly what is meant by exacerbating a complex method, it is noted that claim 1, while embracing generic terminology, does not expressly refer to gene therapy. The present specification teaches several methods, however, including compositions and methods for injecting the M-DNA into an animal such that a gene of interest encoding a desired product, e.g., an antigenic protein or the like, is expressed.

Under "nature of working examples and guidance," (Office action, page 4), the Office recognizes that the specification teaches preparation of M-DNA, and that it demonstrates the M-DNA is nuclease resistant when compared to unmodified DNA. The Office also notes that M-DNA is immunogenic, evidenced by injecting M-DNA into mice and detecting the presence of antibodies to the M-DNA. But the Office Action also states that the disclosure does not provide examples of using M-DNA to express antigenic proteins, nor a showing that the DNA would translate normally. Without knowing this information, according to the Office, the ability to generate an immune response is said to be highly unpredictable.

Applicants submit herewith a Declaration under Rule 132 from Dr. Sylvia van den Hurk. Dr. van den Hurk's Declaration provides evidence that addresses the issue of M-DNA expressing an antigenic protein in an animal. Dr. van den Hurk's experiments employed compositions and teachings described in the instant specification, and are discussed below.

Dr. van den Hurk conducted experiments which demonstrate that M-DNA which encodes an antigenic protein can be expressed in animals, and that the expressed protein will elicit an immune response to the native antigen in the host animals. Dr. van den Hurk prepared M-DNA (both zinc- and nickel-complexed DNA) using an eucaryotic expression vector which contained the tgD gene from bovine Herpes virus. The tgD gene encodes a viral surface glycoprotein. Dr. van den Hurk's Declaration describes in detail (Para. 4) the preparation of the M-DNA and control (B-DNA) "bullets" that were then "shot" into Cos-7 cells (Para. 5). As shown in Para. 6 of her Declaration, Western blotting performed (using a murine monoclonal antibody to tgD) on protein extracted from Cos-7 cells transfected with the tgD expression plasmid via the gene gun confirmed that the tgD protein was expressed in the cells treated with Zn or Ni M-DNA, as well as in control B-DNA treated cells.

To demonstrate that the M-DNA encoded a protein which was could be transcribed and expressed as an immunogenic protein in animals, as explained in Para. 7 of her Declaration, Dr. van den Hurk immunized mice with the plasmid encoding the tgD herpes virus surface glycoprotein, prepared as described in Paras. 4 and 5. Mice were vaccinated on day 1 and boosted on day 28 using a Gene Gun, with plasmid encoding tgD either as B-DNA, or as NiM-DNA or ZnM-DNA. Animals were bled on days 35 and 42 and the serum was tested by standard ELISA for the presence of antibodies specific for the tgD glycoprotein using purified tgD antigen on the plates.

The results of the animal studies are shown in the graph in Para. 7 of Dr. van den Hurk's Declaration. The animals immunized with either Ni or Zn M-DNA produce a sustained antibody response by weeks 5 and 6 which was 2-3 fold higher than that for the control B-DNA.

Dr. van den Hurk's results confirmed that M-DNA prepared according to the present invention can be used in animals to express antigenic proteins, that the M-DNA transcribes normally in animals sufficient to induce an immune response, and the immune response to the M-DNA encoded protein recognizes the native antigen.

Regarding the "state of the art" as mentioned on page 5 of the Office Action, it is noted that the art regarding DNA vaccines is quite well developed, and many patents have been issued in this area for such DNA preparations and compositions. See, e.g., several U.S. Patents issued to Vical Incorporated in recent years (for example, most recently, US 6,710,035; 6,706,694; 6,673,776 and others). Thus, the art is shown to be relatively well developed.

Regarding the "unpredictability of the art," the Office asserts the unpredictability is allegedly high due to the lack of recited methods and because the sequence is unknown at the onset of the invention. Applicants' methods, however, are independent of a particular DNA sequence, so long as the sequence is one capable of engendering a desired physiological response, such as an immune response if that is the result sought. Of course, different sequences have different uses, regardless of the present invention. The worker of ordinary skill will know which sequences to select depending on the intended use. The present invention enhances the resistance of the nucleic acids to nucleases, among other things, thereby facilitating the production of an immune response or other physiological response to the nucleic acid or the transcriptional or translational product thereof. Again, attention is directed to the several patents issued in the art, such as noted above, which are related to methods of delivery and formulations that are typically independent of a particular sequence employed to exemplify the invention.

The remaining comments in the Office Action relate to issues discussed above, i.e., the present invention addresses methods for using metal-complexed nucleic acids that are generally independent of the particular nucleic acid sequence chosen or the species into which the metal-nucleic acid complexes are delivered. The inventors have demonstrated via exemplified embodiments that the metal-complexed sequences have improved resistance to nucleases, and can generate immune responses to the metal-nucleic acid complex or to a protein which is encoded by the nucleic acid of the metal-nucleic acid complex.

Thus, in view of Applicants' teachings, the skilled artisan would not have had to engage in undue experimentation to practice the claimed methods.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: Sept. 10, 2004

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IN THE DRAWINGS:

Figure 2 has been relabeled as Figure 2A and Figure 2B. Copies of the corrected drawing and annotated drawing, showing the correction, are attached hereto.

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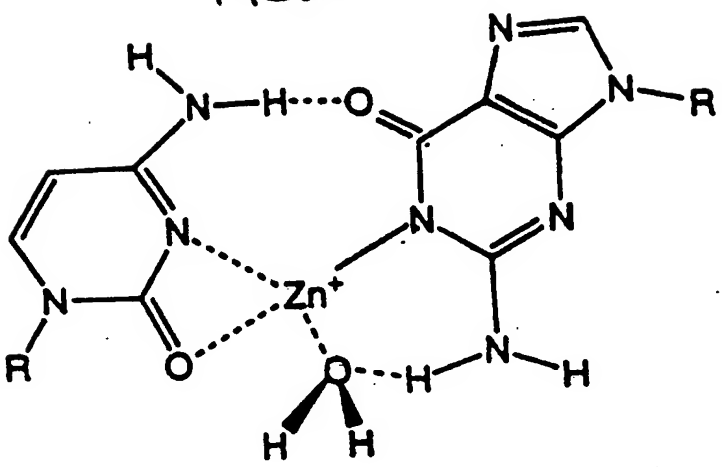
FIGURE 2A



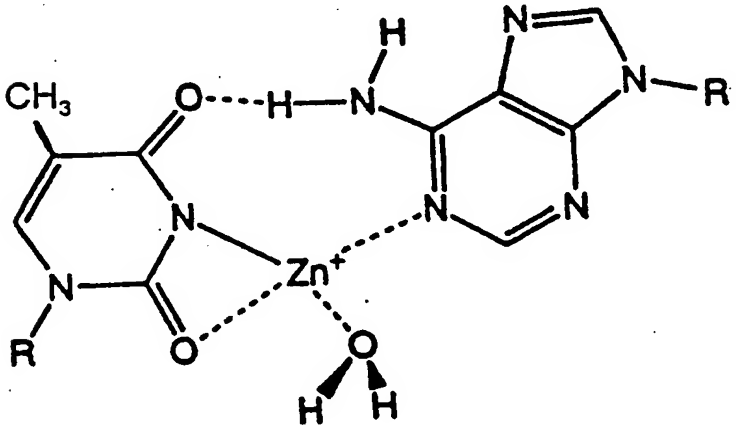


FIGURE 2B

Figure 2